PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: A study protocol
AUTHORS	Safarpour, Ali Reza; Mehrabi, Manoosh; Keshtkar, Abbasali; Edjtehadi, Fardad; Bagheri Lankarani, Kamran

VERSION 1 – REVIEW

REVIEWER	Qin Xiang Ng MOH Holdings Pte Ltd, Singapore
REVIEW RETURNED	18-Jul-2019

GENERAL COMMENTS	The authors should be commended for their detailed study protocol. I have the following major and minor points to raise. 1. The study by C. N. Siew et al is wrongly cited, it should be Ng et al., 2018. It is also unclear how the present study adds to existing literature given the very recent and extensive study by Ng et al., 2018. This should be further explored and substantiated. 2. "definitions of IBD, including CD or UC, based on either the Lennard Jones(7) or Mendeloff's(8) criteria are acceptable." What about the international multicentre scoring system of the Organization Mondiale de Gastroenterologie (OMGE) and the diagnostic criteria of Japanese Research Society on IBD? Furthermore, as these criteria define definite vs probable UC/Crohn's, how will the authors handle this? 3. As this study focused on Asia, it would be important to include Mandarin search terms and to search major Chinese biomedical databases, e.g. the Chinese Biomedical Literature Database (cbm), Chinese Medical Current Content (cmcc), China National Knowledge Infrastructure (cnki, formerly China Academic Journals), vip Information, and Wanfang Data. 4. "will be translated by Google Translate" - is this reliable or sufficient? Should authors engage a Chinese translator instead, especially as this study is centred on Asia. 5. The discussion section could be enhanced with a brief discussion of study limitations. 6. The style of in-text citation is inconsistent e.g. "C. N. Siew et al. in 2018" and "Kelvin T. Thia et al. in 2008". Please correct this.

REVIEWER	Dr Richard C G Pollok St George's Univ. London and St George's Hospital NHS Foundation Trust
REVIEW RETURNED	29-Aug-2019

GENERAL COMMENTS	This is a nicely written protocol with a good overview of the current literature. The authors provide a reasonable justification for a further study beyond that of Siew et al.
	Whilst the authors cite a link to UNSD website it might be helpful to elaborate more fully on the definition of Asia and its subdivisions
	The authors have not mentioned the diagnosis of IBD of undetermined type (IBDU) formally sometimes called indeterminate colitis. I would have thought this should be included since forms part of the group of diagnoses defined as IBD.
	It seems a shame not to have included a paediatric population in this analysis (at least those >6y) since there are important temporal trends in this respect.
	The authors have not described how they will analyse temporal trends in their methodology which should be included. Might it also be worth including a methodology forcasting future trends (see Charlie Lees paper recently published in Gut 2019)
	Details of the dose-response methodology mentioned in the introduction should be described
	I'm not sure a conclusion should be included in a protocol paper according to BMJ Open policy?
	Minor comments
	Pg 17 line 14 should say "will be carried out"
	pg 17 line 24 the second "At this stage" should be removed
	pg 20 line 9 need space after comma

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Thank you very much for your valuable and insightful comments.

Comment #1: The study by C. N. Siew et al is wrongly cited, it should be Ng et al., 2018. It is also unclear how the present study adds to existing literature given the very recent and extensive study by Ng et al., 2018. This should be further explored and substantiated.

Author's response:
• Thank you for your comment. We corrected wrong citation to: Ng et al., 2018(page 5, line 124)

• With all due respect and appreciation for the valuable previous study of Ng et al., 2018, in the last paragraph of the Background section, we have fully outlined the relative advantages of our future systematic review. These are as follows:(Page 6, line 159-169)

1- We registered our protocol as"priori registration" in PROSPERO.
2- We will include all relevant studies regardless of age group (pediatrics or adults) in our review.
3- We will combine data and assess the value and causes of possible heterogeneity if meta-analysis will be possible.
4- We have more inclusive search based on the use of thesaurus systems including Emtree and MeShto detecting the synonym terms.
5- We will conduct our search in large databases such as SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest with a longer search interval.
6- We will use the regional databases such as the Indian Citation Index, Chinese Citation Index, Korean Citation Index andIranMedex, (and according to comment of respected reviewer,the Chinese Biomedical Literature Database, Chinese Medical Current Content, and China National Knowledge Infrastructure).
7- We will use the grey literature, including theses and conference papers and proceedings, and also we will use of experts' views and the examination of key journals, substantially.

The authors hope that by doing above actions, they will be able to conduct a more comprehensive systematic review and meta-analysis by finding further studies.

Comment #2: "definitions of IBD, including CD or UC, based on either the Lennard Jones(7) or Mendeloff's(8) criteria are acceptable." What about the international multicentre scoring system of the Organization Mondiale de Gastroenterologie (OMGE) and the diagnostic criteria of Japanese Research Society on IBD? Furthermore, as these criteria define definite vs probable UC/Crohn's, how will the authors handle this?
Author's response:
Thank you for your comment.
1- We included the two diagnostic criteria for definition and diagnosis of IBD and we have changed the manuscript as below: (Page 3, line 80-83)
The diagnostic criteria stated by two other references included the international multicenter scoring system of Organization Mondiale de Gastroenterologie (OMGE)(9) and the diagnosis criteria of Japanese Research Society on IBD(10) are also acceptable in this study.
New References:
9.Myren J, Bouchier I, Watkinson G, Softley A, Clamp S. The OMGE multinational inflammatory bowel disease survey 1976-1986. A further report on 3175 cases. Scandinavian journal of gastroenterology Supplement. 1988;144:11-9.
10.Shivananda S, Hordijk M, Ten Kate F, Probert C, Mayberry J. Differential diagnosis of inflammatory bowel disease: A comparison of various diagnostic classifications. Scandinavian journal of gastroenterology. 1991;26(2):167-73.

2- We also added definition of "unclassified type of IBD according to two new references as below:(Page 3, line 84-88)
"In the present study, the definition of IBD is acceptable by either of these four criteria, and the ICD-10 diagnostic codes, which are for UC: K51.0-51.9 and CD: K50.0-50.9, are approved for the diagnosis of these diseases. Inflammatory bowel disease, type unclassified (IBDU) will be define according to ICD-10 code: K52.3 and diagnostic criteria revealed by M. Guindi et al.(11) and Ouyang et al.(12)".

New References:
11.Guindi M, Riddell R. Indeterminate colitis. Journal of clinical pathology. 2004;57(12):1233-44.

12.Ouyang Q, Tandon R, Goh K, Pan GZ, Fock K, Fiocchi C, et al. Management consensus of inflammatory bowel disease for the Asia–Pacific region. Journal of gastroenterology and hepatology. 2006;21(12):1772-82.

Comment #3: As this study focused on Asia, it would be important to include Mandarin search terms and to search major Chinese biomedical databases, e.g. the Chinese Biomedical Literature Database (cbm), Chinese Medical Current Content (cmcc), China National Knowledge Infrastructure (cnki, formerly China Academic Journals), vip Information, and Wanfang Data.

Author's response:
•   We appreciate your comment and weadded the statement to the section of "Searching relevant internet resources" as: …and other five large Chinese biomedical bibliographic data bases(27).(Page 6, line 165 and Page 10, line 295-296)
New Reference:
27.   Xia J, Wright J, Adams CE. Five large Chinese biomedical bibliographic databases: accessibility and coverage. Health Information & Libraries Journal. 2008;25(1):55-61.

Comment #4: "will be translated by Google Translate" - is this reliable or sufficient? Should authors engage a Chinese translator instead, especially as this study is centred on Asia.

Author's response:
Thank you for your comment. We will translate the studies by Google Translate system and will recheck by official translators. We added the statement in section of "Language of Publication", (Page 11, line 311) …and recheck by official translators.

Comment #5: The discussion section could be enhanced with a brief discussion of study limitations.

Author's response:
Thank you so much for this comment. We added the limitations of our future study to the manuscript of protocol in (Page17, lines 458-461).
Some of the most important limitations of our future study are: high level of heterogeneity in prevalence studies because of relation of prevalence's studies to the times and places, lack of strong population based studies in most countries of Asian continent and probable methodological bias in included primary studies.

Comment #6: The style of in-text citation is inconsistent e.g. "C. N. Siew et al. in 2018" and "Kelvin T. Thia et al. in 2008". Please correct this.

Author's response:
Thank you for this comment. We corrected all inconsistent citations in background section according to reviewer suggestion as below (Pages 5-6, lines 124, 140, 149,156, 157)
Ng et al., 2018-Molodecky et al., 2012-LaniPrideaux., 2012- Kelvin T. Thia et al., 2008- Jacques Cosnes et al., 2011

Reviewer: 2
Thank you very much for your valuable and insightful comments.

Comment #1: The authors have not mentioned the diagnosis of IBD of undetermined type (IBDU) formally sometimes called indeterminate colitis. I would have thought this should be included since forms part of the group of diagnoses defined as IBD.

Author's response:
- We appreciate your comment and we added the diagnostic criteria of "undetermined type of IBD(IBDU)" to the related part of manuscript:(Page 4, line 86-88).

Inflammatory bowel disease, type unclassified (IBDU) will be define according to ICD-10 code: K52.3 and diagnostic criteria revealed by M. Guindi et al.(11) and Ouyang et al.(12).

New References:
11.Guindi M, Riddell R. Indeterminate colitis. Journal of clinical pathology. 2004;57(12):1233-44.
12.Ouyang Q, Tandon R, Goh K, Pan GZ, Fock K, Fiocchi C, et al. Management consensus of inflammatory bowel disease for the Asia–Pacific region. Journal of gastroenterology and hepatology. 2006;21(12):1772-82.

- And also we have added "undetermined type of IBD(IBDU)" to all related parts of the manuscript, including theabstract, background,objectives, method, definition of diseaseand search syntax and highlighted with yellow color.

Comment #2:It seems a shame not to have included a paediatric population in this analysis (at least those >6y) since there are important temporal trends in this respect.

Author's response:
Thank you for your comment. We included the pediatric population in our protocol and also in future systematic review: …prevalence and incidence of CD and UC and IBDU in patients (with any ages, including pediatrics or adults) in Asia;(Page 7, line 186-187) and also we added that as a relative advantages on (Page6, line 159-160): …review of all relevant studies regardless of age group (including pediatrics or adults),…

Comment #3:The authors have not described how they will analyse temporal trends in their methodology which should be included. Might it also be worth including a methodology forecasting future trends (see Charlie Lees paper recently published in Gut 2019)

Author's response:
Thank you for your comment. We added a paragraph to explain about temporal trend analysis, under the subtitle: Temporal trend analysis, (Page 15, lines 409-417)

Temporal trend analysis
Temporal trends in incidence rate and prevalence during time, will calculate for included studies using join point regression program, Version 4.5.0.1 (Statistical Research and Applications Branch, National Cancer Institute). This program will use the annual prevalence and incidence rate, and identify the years in which changes in the trend of inflammatory bowel disease were occurred (join points), and then with exponentiating beta-coefficients of Poisson regression and subtracting 1, will calculate the annual percentage change (APC) of aforementioned indicators with a 95% CI, between the trend points. The program will also calculate the Average Annual Percentage Change (AAPC) for the entire study period(39, 40).

New References:

39.   Dragomirescu I, Llorca J, Gómez-Acebo I, Dierssen-Sotos T. A join point regression analysis of trends in mortality due to osteoporosis in Spain. Scientific reports. 2019;9(1):4264.
40.   Jones G-R, Lyons M, Plevris N, Jenkinson PW, Bisset C, Burgess C, et al. IBD prevalence in Lothian, Scotland, derived by capture–recapture methodology. Gut. 2019:gutjnl-2019-318936.

Comment #4:Details of the dose-response methodology mentioned in the introduction should be described.
Author's response:
Thank you for your comment. We added a paragraph to explain about "dose-response relationship evaluation" under the subtitle: Dose-Response relationship evaluation, (Page 15, line 398-407)

Dose-Response Relationship Evaluation:
According to previous studies(28, 29, 38), latitude of the countries and their national income per capita(as a proxy of socioeconomic status), may be related to the prevalence or incidence of inflammatory bowel disease. We will calculate these quantitative variables for all Asian countries which have included studies in our systematic review. Then we will change these quantitative variables into three or more categories. Using command DRMETA in STATA software, we will calculate the dose-response relationship between these two variables and the incidence and prevalence of inflammatory bowel disease. Obviously, this calculation is the way to show the relationship of the two variables with the diseases under study and future studies should be consider and evaluate the mediating variables in the disease process.

New Reference:
38.   Ko Y, Kariyawasam V, Karnib M, Butcher R, Samuel D, Alrubaie A, et al. Inflammatory bowel disease environmental risk factors: a population-based case–control study of Middle Eastern migration to Australia. Clinical Gastroenterology and Hepatology. 2015;13(8):1453-63. e1.

Comment #5:I'm not sure a conclusion should be included in a protocol paper according to BMJ Open policy?
Author's response:
Thank you for your comment. According to BMJ's instructions to author in address:https://bmjopenrespres.bmj.com/pages/authors/#protocol, conclusion is not a part of the protocol manuscript.

VERSION 2 – REVIEW

| REVIEWER | Qin Xiang Ng
MOH Holdings Pte Ltd |
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| REVIEW RETURNED | 18-Sep-2019 |

| GENERAL COMMENTS | Specific comments:
- Please change "The protocol of this systematic review and meta-analysis was prepared according to the 204 recommendations from the CRD's guideline" to "The protocol for this systematic review and meta-analysis was prepared according to the recommendations from the CRD's guidelines".
- Do you mean "MOOSE" guidelines and not MOOS. Please spell this abbreviation out in full as well in the first instance of its use.
- "The minimum acceptable sample size for the preliminary studies is 30." How did the authors arrive at this number?
- For future work, authors could also study the co-occurrence of IBD and IBS symptoms. Approximately 20% of patients with IBD can have concurrent IBS symptoms and there are limited Asian studies done to investigate this (citation: |
| --- | --- |

	ncbi.nlm.nih.gov/pmc/articles/PMC6159811). This is an interesting area for investigation.
	- Ref [29] seems wrong. Please check. It should be "Gastroenterology. 2013 Jul;145(1):158-165.e2. doi: 10.1053/j.gastro.2013.04.007."
	- "We acknowledge vice chancellor of research of Shiraz University of 482 Medical Sciences." Be specific. Who is the vice-chancellor and what is he or she acknowledged? What was his or her role?

VERSION 2 – AUTHOR RESPONSE

We are very grateful for the reviews provided by the editors and the reviewers of this manuscript. The encouraging comments are accepted by all authors.

VERSION 3 – REVIEW

REVIEWER	Qin Xiang Ng MOH Holdings Pte Ltd, Singapore
REVIEW RETURNED	14-Oct-2019

GENERAL COMMENTS	Thank you for the revisions.